Clinical Pharmacokinetic of Aminoglycoside antibiotics .

Done by:

1- Rezg Youssif Hassan Al-Sunah.

2- Edress Abdullah Ahmed Aidan.

3- Mohammed Abbas Hawash;

4- Abdul Rahman Saad Al-Mekhlafi

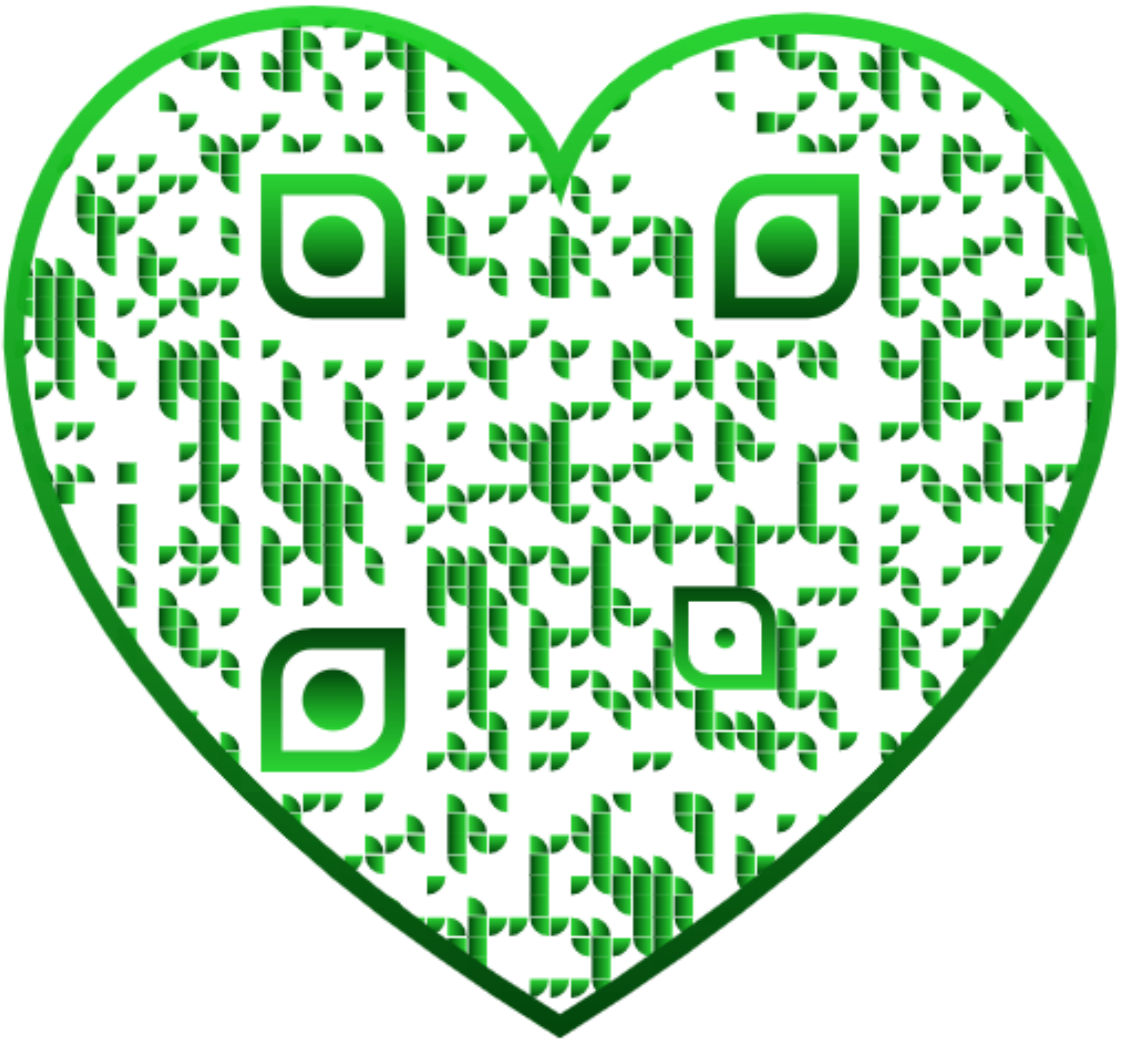
5- Abdul Khaliq Ali Al-Ammari

6- Mohammed Adel Al-Hatami.

7- Fathi Anis Qabati

Supervisor: Asst Prf. *Mahmoud Mahyoob Alburyhi.*

Clinical Pharmacy Faculty, L4, EIU



Introduction:-

- Aminoglycoside antibiotics include gentamicin, tobramycin, amikacin and streptomycin.

- Gentamicin is commonly used to treat infections caused by Gram-negative bacilli, Gram positive bacilli and Gram positive cocci, such as Escherichia coli, Proteus species, Pseudomonas aeruginosa, Serratia species, Enterobacter species, Citrobacter species, and Staphylococcus species (coagulase-positive and coagulase-negative).

- It was approved by FDA to be used in combination with ampicillin as empirical therapy for sepsis in newborns and infants. It has also been used for the peritonitis in patients with peritoneal catheters.

Introduction:-

- Amikacin is commonly used for treatment of serious infection (bone and respiratory infections, endocarditis and septicaemia) due to organism resistant to Gentamicin and Tobramycin including Pseudomonas, Klebsiella, Enterobacter, Serratia, Proteus and Providencia species, and Escherichia coli.

- It has also been used for documented infection of susceptible mycobacterial organisms.

Target Concentration Range For Selected Aminoglycoside

Dosing	Gentamicin (mg/L)		Amikacin (mg/L)	
	TROUGH	PEAK	TROUGH	PEAK
Neonates	< 1	5 – 12	< 5	20 – 30
MDD	<2	5 – 10	<10	20 – 30
SDD	< 1	10 – 30*	< 1	60*
Synergy	<1	3 – 5	N/A**	N/A**
Hemodialysis	<2	Not necessary	<10	Not necessary

The target concentration ranges vary and may be individualized based on institutional MIC value to achieve peak to MIC ratio of 10:1.

**N/A: Not Available

KEY PARAMETERS:

Therapeutic Range	Refer to 'Target concentration range for selected Aminoglycoside
Bioavailability (F)	Oral: < 10% Intramuscular & Intravenous: ~100%
Volume of Distribution (Vd)	Adult: 0.2 – 0.3 L/kg Pediatrics: 0.3 – 0.5 L/kg
Clearance (CL)	100% unchanged in the urine
Half-life (t1/2)	1.5 – 3 hours

PHARMACOKINETICS

- **Bioavailability:**
  - **Oral: < 10%**
  - **Intramuscular & Intravenous: ~100%**

- **Volume of Distribution (Vd):**

Neonates	0.4 – 0.6 L/kg
Pediatrics	0.3 – 0.5 L/kg
Adult	0.2 – 0.3 L/kg
Obesity (>30% over IBW)	0.26 [IBW + 0.4 (TBW – IBW)]
Cystic fibrosis	0.35 L/kg

PHARMACOKINETICS

- **Clearance (Cl):**
  - **Elimination: Totally unchanged in the urine.**
  - **Clearance is directly related to renal function**
  - **Hemodialysis clearance: Gentamicin ~50%, Amikacin ~20% (variable; dependent on filter, duration, and type of HD)**

- **Factors that may influence Vd or/and Clearance:**

Increase Vd	Ascites, burn patient, cirrhosis, cystic fibrosis, critically ill, pancreatitis, Patent Ductus Arteriosus, post-surgery
Reduce Vd	Dehydration
Increase Cl	Burn patient, cystic fibrosis, dialysis, critically ill
Reduce Cl	Cirrhosis, prematurity, Patent Ductus Arteriosus

PHARMACOKINETICS

- **Half-life (t½):**

Neonates (<1 week)	3 – 11.5 hours
Infant (>1 week- 6 months)	3 – 3.5 hours
Adult	1.5 – 3 hours
Adult – Renal failure	50 hours (36 – 72 hours)
Adult – Obese	2 – 3 hours
Burn	1.5 hours

DOSAGE

DOSING STRATEGIES

- A. SINGLE DAILY DOSING (SDD).
    1) Approach 1: SDD Initial Dosing
    2) Approach 2: SDD Initial Dosing based on Hartford Nomogram
- B. CONVENTIONAL DOSING
- C. SYNERGISTIC DOSING

DOSAGE

A. SINGLE DAILY DOSING (SDD).

- **Single daily dose Based on their concentration-dependent bactericidal action.**
- **Aminoglycoside demonstrates more rapid bacterial killing by achieving a high peak concentration approximately ten times the MIC necessary for bacterial growth inhibition.**

- **Besides that, administration of larger and less frequent doses produce trough concentration lower than assay sensitivity limit (drug free period) between dose intervals which provides:**
  - **Possibly less nephrotoxicity event by decreasing renal cortical Aminoglycoside concentrations.**
  - **Continued suppression of bacterial growth between 2 – 8 hours despite concentration falling below MIC (Post antibiotic effect.**

  Less development of adaptive resistance by allowing a recovery period during the dosing interval defined as a recovery period before organisms can resume growth after drug removal.

DOSAGE

A- SINGLE DAILY DOSING (SDD).

- **Due to pharmacokinetic alterations, clinical judgement should be used when using SDD for the following populations:**

- Pregnancy (Pregnancy Category D).
- Ascites
- Gram positive infections
- Dialysis
- Hemodynamically unstable patients
- Only use when benefit outweighs risk
- Burns
- Creatinine clearance <30 ml/min
- Neutropenic patients
- Cystic fibrosis

DOSAGE

Approach 1: SDD Initial Dosing

- In general, the adult gentamicin and amikacin dose for SDD in patients with normal renal function is 4 – 7 mg/kg/day and 15 – 20 mg/kg/day respectively.

- Based on renal function, the initial SDD dose is as follows:

Creatinine Clearance (ml/min)	Dose [7]	
	Gentamicin	Amikacin
> 80	5.1 mg/kg q24h	15 mg/kg q24h
60 – 80	4 mg/kg q24h	12 mg/kg q24h
40 – 60	3.5 mg/kg q24h	7.5 mg/kg q24h
30 – 40	2.5 mg/kg q24h	4 mg/kg q24h
20 – 30	4 mg/kg q48h	7.5 mg/kg q48h
10 – 20	3 mg/kg q48h	4 mg/kg q48h
0 – 10	2 mg/kg q72h & AD*	3 mg/kg q72h & AD*

DOSAGE

Approach 2: SDD Initial Dosing based on Hartford Nomogram.

- **Using SDD pharmacodynamics concepts, Hartford method suggests initial use fixed dose of 7 mg/kg of gentamicin and 15 mg/kg of amikacin.**

- **However, due to utilization of relatively high dose (especially for gentamicin), one should consider suitability of practising this nomogram in local population before its application.**

Creatinine Clearance (ml/min)	Dose interval (hours)
≥60	24
40 – 59	36
20 – 39	48
<20	Monitor serial concentration, re-dose when <1 mg/L

DOSAGE

B. CONVENTIONAL DOSING:-

- **Conventional dosing is an approach of administering smaller and more frequent doses usually given every 8 – 12 hours or approximately two to three times the half-life.**

- **This dosing is commonly given in patients with significant pharmacokinetics alterations as stated in SDD exclusion criteria.**

Creatinine Clearance (ml/min)		Gentamicin	Amikacin
>60[8]		1.5 – 2 mg/kg every 8 hourly	5 – 7.5 mg/kg every 8 hourly
40 – 60[8]		1.5 – 2 mg/kg every 12 hourly	5 – 7.5 mg/kg every 12 hourly
20 – 40[8]		1.5 – 2 mg/kg every 24 hourly	5 – 7.5 mg/kg every 24 hourly
<20[8]		1.5 – 2 mg/kg every 48 – 72 hourly*	5 – 7.5 mg/kg every 48 – 72 hourly
RENAL REPLACEMENT DOSING	HD[3]	Loading dose: 2 – 3 mg/kg followed by 1 – 2 mg/kg every48 – 72 hourly*	5 – 7.5 mg/kg followed by every 48 – 72 hourly*
	CRRT [3][9]	Loading dose: 3 mg/kg followed by: 2 mg/kg every 24 – 48 hourly*	Loading dose: 10 mg/kg followed by: 7.5 mg/kg every 24 – 48 hourly*
	CAPD[10]	Intermittent: IP 0.6 mg/kg daily (1 exchange daily) Continuous: LD IP 8 mg/L then MD 4 mg/L in all exchanges	Intermittent: IP 2 mg/kg daily (1 exchange daily) Continuous: LD IP 25 mg/L then MD 12 mg/L in all exchanges

DOSAGE

C. SYNERGISTIC DOSING:-

- Synergy dosing is a low dose of Aminoglycoside in combination with an antimicrobial agent (i.e. beta-lactams, glycopeptides) against Gram – positive bacterial infections (eg: endocarditis);

CrCl (ml/min)	Dose of Gentamicin
>60	1 mg/kg every 8 hourly
40 – 60	1 mg/kg every 12 hourly
20 – 40	1 mg/kg every 24 hourly
<20	1 mg/kg load*
HD	1 mg/kg every 48 – 72 hourly*
CRRT	1 mg/kg every 24 – 36 hourly*

AMINOGLYCOSIDE DOSING STRATEGIES –NEONATES

1- Gentamicin

Dosing Chart

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤ 29	0 – 7 8 – 28 ≥ 29	5 4 4	48 36 24
30 - 34	0 – 7 ≥ 8	4.5 4	36 24
≥ 35	ALL	4	24

AMINOGLYCOSIDE DOSING STRATEGIES –NEONATES

1- Gentamicin

Suggested Dosing Intervals

Concentration at 24 hours (mg/L)	Half-life (hours)	Suggested Dosing Interval (hours)
≤1	~8	24
1.1 to 2.3	~12	36
2.4 to 3.2	~15	48
≥ 3.3	-	Measure concentration in 24 hours

AMINOGLYCOSIDE DOSING STRATEGIES –NEONATES

2) Amikacin:-

Postmenstrual Age Dosing Chart a

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤ 29	0 – 7 8 – 28 ≥ 29	14 12 12	48 36 24
30 - 34	0 – 7 ≥ 8	12 12	36 24
≥ 35	ALL	12	24

[a] Target trough: <8 mg/L, peak: 20-35 mg/L

AMINOGLYCOSIDE DOSING STRATEGIES –NEONATES

2) Amikacin:-

Weight Dosing Chart b

Weight (g)	Postnatal Age			
	Younger than 14 days		14 days or older	
	Dose (mg/kg)	Interval (hours)	Dose (mg/kg)	Interval (hours)
< 800	16	48	20	42
801-1200	16	42	20	36
1201-2000	15	36	18	30
2001-2800	15	36	18	24
>2800	15	30	18	20

b Target trough: <3 mg/L, peak: >24 mg/L

AMINOGLYCOSIDE DOSING STRATEGIES –NEONATES

2) Amikacin:-

Suggested Dosing Intervals

Concentration at 24 hours (mg/L)	Half-life (hours)	Suggested Dosing Interval (hours)
≤5	~9	24
5.1 to 8.0	~12	36
8.1 to 10.5	~16	48
≥10.6	Not Available	Measure concentration in 24 hours

AMINOGLYCOSIDE INTERACTIONS.

Aminoglycoside use with the following drugs/conditions/disease may potentiate toxicity.

Nephrotoxicity	Ototoxicity
Concomitant Drugs	
• Amphotericin B • Cyclosporine • Diuretics (eg: Frusemide) • Other nephrotoxic drugs • Vancomycin	• N/A
Condition/disease	
• Advanced age • Dehydration • Pre-existing renal impairment	• Hearing loss • Tinnitus • Vertigo

AMINOGLYCOSIDE MONITORING PARAMETER

- **Obtain serum concentrations if there are changes in renal function.**
- **Patient clinical characteristics such as**
  - **Renal function: creatinine and urea levels**
  - **Hydration status, input & output fluid balance**
  - **Temperature**
  - **White blood cell count**
- **Culture & sensitivity.**
- **Sign and symptoms of auditory or vestibular toxicity**

AMINOGLYCOSIDE ADVERSE DRUG REACTIONS;

- **Increase risk of**

1- ototoxicity (auditory/vestibular),

2- nephrotoxicity

3- neurotoxicity (eg: vertigo and ataxia).

AMINOGLYCOSIDE DILUTION AND ADMINISTRATION

- **Dilution of drug:**

Amikacin	• Diluent: Normal saline or Dextrose 5% • 500 mg/vial – diluted into 100 – 200 ml of diluent • Concentration: 0.25 – 5 mg /ml
Gentamicin	• Diluent: Normal saline or Dextrose 5% • Diluted into 100 – 200 ml of diluent

- **Drug administration:**

Intravenous Infusion	• 30 – 60 minutes
Intravenous Bolus	• Administer slowly over 2 – 3 minutes
Intramuscular	• Administer undiluted into a large muscle mass

AMINOGLYCOSIDE Calculations

A- ESTIMATING INITIAL DOSE BASED ON POPULATION PHARMACOKINETICS

1. **Determine the dosing weight:**

$$IBW\,(Male) = 50kg + 0.9(Ht - 152cm)$$

$$IBW\,(Female) = 45.5kg + 0.9(Ht - 152cm)$$

$$Adjusted\,body\,weight = IBW + 0.4(ABW - IBW)$$

- Compare ABW to IBW
- Determine if use either ABW, IBW or Adjusted BW for dosing weight based on:

- *If ABW/IBW is > 0.9 to < 1.2* — *Use ABW*
- *If ABW/IBW is > 1.2* — *Use Adjusted body weight*
- *If ABW/IBW is > 0.75 to < 0.9* — *Use IBW*
- *If ABW/IBW is ≤ 0.75* — *Use ABW x 1.13*

AMINOGLYCOSIDE Calculations

A- ESTIMATING INITIAL DOSE BASED ON POPULATION PHARMACOKINETICS.

2) Determine the volume of distribution (Vd):

$$\text{Vd (L)} = \text{Population Vd (L/kg)} \times \text{Dosing Weight (kg)}$$

3) Estimate creatinine clearance (CrCl):

$$\text{CrCl(ml/min)} = \frac{(140 - age) \times 1.04\ (F)\ or\ 1.23\ (M)}{Scr\ (\mu mol/L)}$$

4) Estimate aminoglycoside clearance(CLamg):

$$\text{CLamg(L/hr)} = \text{CrCl(ml/min)} \times \frac{(60min)}{1000/ml)}$$

5) Estimate elimination rate constant (Ke):

$$\text{Ke(hr}^{-1}) = \frac{\text{CLamg(L/hr)}}{Vd\ (L)}$$

AMINOGLYCOSIDE Calculations

A- ESTIMATING INITIAL DOSE BASED ON POPULATION PHARMACOKINETICS.

6) Estimate half life (t1/2):

$$t½\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

7) Estimate dosing interval (τ):

$$\text{Dosing interval}, \tau\ (hr) = \frac{ln\ target\ Cmax - ln\ target\ Cmin}{ke}$$

8) Estimate initial dose by deciding target Cmax:

$$\text{Initial dose (mg)} = \text{Target Cmax (mg/L)} \times \text{Vd (L)} \times (1 - e^{-K e \tau})$$

9) Estimate expected Cmax and expected Cmin concentration:

$$Expected\ Cmax\ (mg/L) = \frac{Dose\ (mg)}{Vd\ (L) \times (1 - e - Ke\tau)}$$

$$\text{Expected Cmin (mg/L)} = \text{Expected Cmax} \times e^{-K e \tau}$$

CASE DISCUSSION

- **ABC (45 years old male, 175 cm, 130 kg) was diagnosed with Hospital-acquired pneumonia (HAP) and was in septic shock. Tracheal C&S innoculated Pseudomonas aeruginosa. IV Cefepime 2g TDS was started for HAP. Doctor would like to add IV Amikacin as dual therapy. What is your recommendation for Amikacin starting dose?**

Lab values: Urea=4.0 mmol/L, Scr =110 µmol/L, WBC=25x10^9/L, CRP=213 mg/L

AMINOGLYCOSIDE Calculations

A- Single Daily Dose (SDD): When two post sampling concentrations are available.

(Recommended sampling: Post 2 hour (C2) & post 6 hour (C6))

1) Estimate elimination rate constant (Ke):

$$Ke\ (hr{-}1) = \frac{ln\ C2 - ln\ C6}{t6 - t2}$$

2) Estimate half life (t1/2):

$$t½\ (hr) = \frac{0.693}{Ke\ (hr{-}1)}$$

3) Estimate the expected Cmax concentration:

Used when sample was taken at a time beyond the expected peak, assuming peak concentration occurs 1 hour after start of administration.

$$Cmax = Cpost\ (C2) \times eKet'$$

AMINOGLYCOSIDE Calculations

A- Single Daily Dose (SDD): When two post sampling concentrations are available.

4) Estimate the expected Cmin concentration:

$$Cmin = Cmax \times e^{-Ke\tau}$$

5) Determine the volume of distribution (Vd):

$$Vd\ (L) = \frac{Dose\ (mg)}{Cmax\ (1 - e^{-Ke\tau})}$$

6) Calculate the Drug Free Period (DFP): (Ensure DFP within 2 – 8 hours. If exceeds 8 hours, consider adjust interval/dose)

- First, calculate the time required for Cmax to fall to MIC (tMIC)

$$tMIC\ (hr) = \frac{ln\ Cmax - ln\ C\ MIC}{Ke}$$

$$DFP\ (hr) = \tau - tmax - tMIC$$

Assume tmax =1 (1 hour after start of administration)

CASE DISCUSSION

- GHI (24 years old male, 176 cm, 64 kg) was diagnosed with pyelonephritis. Urine and pus C&S showed Pseudomonas aeruginosa sensitive to Gentamicin (MIC=0.5 mg/L). Doctor prescribed IV Gentamicin 240 mg OD for him. Post 2 hours sample and post 6 hours sample were drawn after 2nd dose of IV Gentamicin at 5/1/19, 12 pm. Infusion time for Gentamicin was 1 hour.

- Lab values: Urea=2.2 mmol/L, Scr=76 µmol/L, WBC=15x10^9/L, CRP=60 mg/L
- TDM results as follows:

Gentamicin	Sampling Time	Gentamicin Concentration
Post 2 hours sample	5/1/19, 2 pm	12.2 mg/L
Post 6 hours sample	5/1/19, 6 pm	4.8 mg/L

Thank you

By/ Rezg AL-Sunah